PURPOSE:

The purpose of this policy is to describe the process for the monitoring of accrual for all protocols conducted within the Clinical Trials Office (CTO) of St. Luke's University Health Network (SLUHN).

In an effort to ensure appropriate utilization of SLUHN CTO resources and protect patient safety, trials shall be evaluated for accrual issues and recommended for closure as appropriate.

Also, per FDA Guidance review for accrual, it is the IRB's responsibility to protect human subjects, which should include the IRB's review of trial progress. Information about the number of subjects enrolled in the overall trial may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the approved protocol. If enrollment in the study as a whole is too low, it may not be possible for the study to meet its stated objectives, and therefore the study may no longer be ethical because the risks to subjects may exceed the anticipated benefits. That is, there may not be justification to continue exposing subjects to the risks of the test article because the study itself may no longer be expected to provide sufficient data to answer the scientific question at hand. To address low enrollment issues, it may be recommended that the reasons behind the lagging enrollment be explored and appropriate steps be taken to remedy the situation as outlined in this policy.

DEFINITIONS/ABBREVIATIONS:

- **Accrual Goal:** 20 percent of target enrollment per year the trial has been open. For example, Trial A has a target accrual of 10 patients and has been open for 2 years; to meet the accrual goal of this policy, the trial shall have enrolled 4 patients.
- **Central Institutional Review Board (CIRB):** A centrally managed IRB developed by the NCI to allow for more effective and efficient centralized review of national multi-site NCTN clinical trials.
- **Clinical Trials Office (CTO):** Centralized clinical trials staff, responsible for the conduct and support of SLUHN clinical trial functions
- **Close Out Visit (COV):** A visit, either onsite, remote, or via phone, conducted by the sponsor of a trial to review all trial documents and activity, as well as any ongoing requirements, before a trial is officially closed at a site.
- **Data Doctor Office Technology Systems, Inc. (DDOTS):** Clinical Trials Management System utilized by the SLUHN CTO
- **Food and Drug Administration (FDA):** Agency of the United States Department of Health and Human Services (DHHS), responsible for the regulation of clinical trials.
- **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of research that provides assurance

that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of subjects are protected.

- **Informed Consent Form (ICF):** IRB approved form outlining all aspects of a clinical trial in lay language, signed by the subject consenting to participate in the clinical study.
- **Institutional Review Board (IRB):** Independent ethics committee formally designated to approve, monitor, and review biomedical and behavioral research involving human subjects.
- **Investigator-Initiated Trial (IIT):** A clinical trial, either funded or unfunded, that is written by an SLUHN physician serving as both the PI and regulatory sponsor of the trial.
- **National Clinical Trials Network (NCTN):** A National Cancer Institute (NCI) program that gives funds and other support to cancer research organizations to conduct cancer clinical trials. The groups in the NCTN include the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, SWOG, Children's Oncology Group (COG), and the NCI of Canada-Clinical Trials Group (NCIC-CTG). The NCTN was previously known as the NCI Clinical Trials Cooperative Group Program.
- **Principal Investigator (PI):** Lead investigator, responsible for the sound conduct of the project in accordance with the protocol and regulations.
- **St. Luke's University Health Network (SLUHN)**

SCOPE:

This SOP applies to all clinical trials site personnel involved in the conduct of clinical trials within the SLUHN.

This policy describes the process:

- Starting from the time a trial is reviewed for feasibility
- Ending with final close-out (e.g. termination with the IRB)

This policy is applicable to the following studies:

- All clinical trials conducted within the SLUHN CTO

PERSONNEL RESPONSIBLE:

This SOP applies to those members of the clinical research team involved in reviewing, conducting, and managing clinical trials at SLUHN. This includes the following:

- Principal Investigator (PI)
- Clinical Trials Management
- SLUHN IRB
- CTO Staff

ROLES:
The following information describes which areas and associated roles that shall adhere to this policy:

Director of Clinical Trials and Research: The Director of Clinical Trials and Research, along with the IRB, shall be responsible for reviewing all Accrual Policy Exemption requests and providing the PI with exemption decision. The Director of Clinical Trials and Research, along with the SLUHN IRB, shall also be responsible for the annual review of all clinical trials that have not accrued 20 percent of their target accrual for each year that the trial has been actively open for enrollment based on the summary of review and recommendations from the PI and Clinical Trials Manager. The Director of Clinical Trials and Research or designee shall also be responsible for distributing a Closure Letter to the PI and IRB.

Clinical Trials Manager: The Clinical Trials Manager or designee shall be responsible for collecting target accrual information and Accrual Policy Exemption Requests, a signed New Study Feasibility Checklist, and signed Accrual Policy from the PI and providing this information to the Study Start-up Project Coordinator. All Accrual Policy Exemption Requests must also be provided to the Director of Clinical Trials and Research for approval.

The Clinical Trials Manager or designee shall also be responsible for assuring that all patient accrual information is entered into the Trial Portfolio Log and DDOTS on a weekly basis, and all accrual information is up-to-date. They shall also be responsible to review trial accrual on a monthly basis and identify any trials that have not accrued 20 percent of their target accrual for each year that the trial has been actively open for enrollment, and communicate accrual issues with the PI of such trials to determine whether the PI wishes to keep the trial open or close the trial. This review, including the PI decision and justification to keep a trial open (if applicable), shall be completed at least 3 months prior to IRB periodic review, and shall be supplied to/discussed with the Director of Clinical Trials and Research for review.

Principal Investigator or designee: The Principal Investigator shall be responsible for carefully reviewing new potential trials for accrual feasibility, and providing their target accrual estimate. If opening a new trial and requesting exemption from the accrual closure policy, the PI shall also be responsible for providing a clear justification as to why the trial meets the exemption criteria and obtaining sign-off by the department Chair.

Study Start-up Project Coordinator: The Study Start-up Project Coordinator shall be responsible for maintaining all signed New Study Feasibility Checklists, signed Accrual Policies, and Accrual Policy Exemption Request Forms, and updating the Trial Portfolio with all necessary information. The Study Start-up Project Coordinator shall also be responsible for updating and maintaining the Accrual Exemption Log, and informing the Director of Clinical Trials and IRB of all Accrual Policy Exemption Requests.

Regulatory Coordinator: The Regulatory Coordinator shall be responsible for the submission of Periodic Reviews that may include PI justifications to keep a trial open, accrual closure requests, and Final Reports to the IRB as necessary.

IRB: The IRB, along with the Director of Clinical Trials and Research, shall be responsible for reviewing all Accrual Policy Exemption requests and providing the PI with exemption decision. The IRB shall also be responsible for ensuring trials are closed within 60 days of the Closure request letter being distributed by the Director of Clinical Trials and Research or designee.

PROCEDURES:

- All new clinical trial protocols supported by the SLUHN CTO are added to the appropriate Trial Portfolio Log and DDOTS by the Study Start-up Project Coordinator.
- Target Accrual information and Exemption Requests shall be provided by the PI to the Clinical Trials Manager.
- A signed (by the PI) New Study Feasibility Checklist and signed Accrual Policy will be obtained by the Clinical Trials Managers or designee and provided to the Study Start-up Project Coordinator, as well as to the IRB along with the initial IRB Application submitted by the Study Start-up Project Coordinator.
- Accrual Policy Exemption requests will be provided to and reviewed by the Director of Clinical Trials and Research and the IRB Administrator, and will be collaboratively approved or denied.

  NOTE: All CIRB NCTN oncology trials may be automatically exempt from this policy; however, must enroll at least 1 patient in 3 years per the accrual exemption requirements.
- The Study Start-up Project Coordinator will enter the target accrual information and Exemption determination in the Trial Portfolio Log and DDOTS, and all patient accrual data will also be entered on a weekly basis by the Clinical Trials Managers.
- Accrual Policy Exemptions will also be added to the Accrual Exemption Log by the Study Start-up Project Coordinator.
- The Manager shall review accrual on a monthly basis to identify any trials that have not accrued 20 percent of their target accrual for each year that the trial has been actively open for enrollment, and accrual issues shall be communicated with the PI to determine whether the PI wishes to keep the trial open or close the trial. This review, including the PI decision and justification to keep a trial open (if applicable), shall be completed at least 3 months prior to IRB periodic review, and shall be supplied to/discussed with the Director of Clinical Trials and Research for review. Trials not meeting target accrual will be reviewed at the time of IRB Periodic Review, and the Director of Clinical Trials and Research, along with the SLUHN IRB, shall have the authority to suspend or close a trial due to accrual issues.

- Trials that are exempt from this policy shall also be closed if there is zero accrual after three years.
- The PI of any non-exempt trial that has not accrued 20 percent of the total accrual goal for each year that the trial was open will be notified of their accrual status by the Clinical Trials Manager, in which they will be given 5 days to respond. If no response is received, the trial will automatically be closed by the IRB and SLUHN CTO.
- The PI response should include one of the following responses:
  - An agreement to close the trial,
  - A detailed plan of action to increase accrual, or
  - A detailed justification of why the trial should be "Exempt" from the closure policy. All Exemption requests must be approved by the department Chair, and will be reviewed and either approved or denied by the Director of Clinical Trials and Research and the IRB
- Trials that are not exempted from the policy and justified to remain open by the PI, will be re-reviewed during the next annual Periodic Review.
- The trial will be closed if it still has not accrued 20 percent of the total accrual for each year it has been open to enrollment. This will allow the PI an entire year to become compliant with the accrual policy.
- Any trials that are not exempt from this policy, and have been open to enrollment for 2 years or more with zero accrual will automatically be closed.

INITIAL EXEMPTION

Role	Step	Activity
PI	1.0	Provide the Clinical Trial Manager with target accrual, signed New Study Feasibility Checklist (***Attachment A***), signed Accrual Policy, and signed Accrual Policy Exemption Request (***Attachment B***) if applicable. **NOTE:** All CIRB NCTN oncology trials may be automatically exempt from this policy; however, must enroll at least 1 patient in 3 years per the accrual exemption requirements.
Clinical Trials Manager	1.1	Provide the Study Start-up Project Manager with all documents from Step 1.0, and also provide all Accrual Policy Exemption Requests (if seeking exemption from this policy) signed by the department Chair, to the Director of Clinical Trials and Research. **NOTE:** Exemption Categories are as follows: o Institutional Priority (e.g. grant funded, translational research, FDA-regulated IIT, SLUHN faculty National PI) o Rare Disease

		○ Observational Trial **NOTE:** Only ***two*** exempt trials ***per year*** (rolling 12 months) ***per PI*** will be approved for exemption from this policy.
Director of Clinical Trials and Research/IRB	1.2	Review Exemption requests and approve or disapprove, and inform PI of decision.
Study Start-up Project Coordinator	1.3	Upload trial information into Trial Portfolio Log, including target accrual and exemption determination. **NOTE:** If Exemption is requested, the Accrual Exemption Log (***Attachment C***) shall also be updated.
Clinical Trials Manager	1.4	Update accrual numbers in Trial Portfolio Log on a weekly basis

ACCRUAL REVIEW OF EXEMPT TRIALS

Timeframe	Role	Step	Activity
Yearly (at least 3 months prior to IRB Periodic Review)	Clinical Trials Manager	2.0	Run report of SLUHN trials that are Exempt from Accrual Policy
	Clinical Trials Manager	2.1	Inform Director of Clinical Trials and Research of any exempt trials that have been open to enrollment for three years with zero accrual
	Director of Clinical Trials and Research/IRB	2.2	Inform the PI that the trial will be terminated due to lack of accrual via Closure Letter ***(Attachment D)***
	Regulatory Coordinator	2.3	Prepare and submit Final Report to IRB **NOTE:** Close Out Visit (COV) shall be scheduled if applicable (e.g. Industry sponsored Trials) prior to Final Report submission
	IRB	2.4	Close the trial within 60 days of Closure Letter date

ACCRUAL REVIEW OF NON-EXEMPT TRIALS

Timeframe	Role	Step	Activity
Monthly (3 months prior to IRB Periodic Review)	Clinical Trials Manager	3.0	Review Trial Portfolio Log for accrual status.
	Clinical Trials Manager	3.1	Review accrual percentages based on target accrual number, and identify any studies that have not accrued 20 percent of their total target accrual for each year that the trial has been open.

	Clinical Trials Manager	3.2	Provide a summary of review and recommendations based on accrual status to the PI and Director of Clinical Trials and Research within 5 working days. **NOTE:** Trials that have zero accrual and have been open to enrollment for at least 2 years will be reviewed by the Director of Clinical Trials and Research, along with the IRB Administrator, and will be closed immediately with a Closure Letter sent to PI **(see Steps 2.2 to 2.4)**.

PI RESPONSE

Timeframe	Role	Step	Activity
Within 5 Working Days of Initial Accrual Communication	PI	4.0	Review accrual status with Manager.
	PI	4.1	Provide a response to the Clinical Trials Manager with one of the following decisions: • Agreement to close trial • Action Plan to meet accrual standards (e.g. adjust target accrual number, amend eligibility criteria, change in personnel or infrastructure, etc.) • Justification as to why the trial should be exempt from this policy signed by Department Chair **NOTE:** Requests for Exemption will be reviewed by the Director of Clinical Trials and Research and IRB (**see Steps 1.1 through 1.4**)
	Clinical Trials Manager	4.2	Inform CTO study team of PI decision from Step 4.1 **NOTE:** If PI wishes to keep trial open, Clinical Trials Manager shall provide a copy of the Justification to keep trial open to the Director of Clinical Trials and Research for review prior to proceeding to Step 4.3 **NOTE:** Justification date shall be entered in the Trial Portfolio Log
	Regulatory Staff of CTO	4.3	<u>Closure Decision:</u> Submit a Final Report or an amendment to close the trial to enrollment (if patients are still active)if no response is received by the PI within 5 working days, or of the PI agrees to close the trial. <u>Keep Open:</u> Submit PI Justification and Accrual Action

			Plan with Periodic Review. **NOTE:** COV shall be scheduled if applicable (e.g. Industry sponsored Trials) prior to Final Report submission
	IRB	4.4	Review PI Responses during Periodic Review.
	IRB	4.5	Rule to either close the trial immediately or grant an extension for accrual compliance at which time the trial will be re-reviewed during next IRB Periodic Review.
	Regulatory Staff of CTO	4.6	Submit any necessary amendments to the IRB based on PI action plan.
	IRB Administrator	4.7	Send appropriate correspondence to the Director of Clinical Trials and Research and the PI regarding decision to either close the trial or grant an extension.

ACCRUAL RE-REVIEW

Timeframe	Role	Step	Activity
Monthly (At least 3 months prior to next Periodic Review)	Clinical Trials Manager	5.0	Review Trial Portfolio Log for accrual status. **NOTE:** Repeat Steps 3.1 through 4.7 for new trials not previously approved to remain open via the justification process.
	Clinical Trials Manager	5.1	Review accrual percentages based on target accrual number, and identify any studies that have not accrued 20 percent of their total target accrual for each year that the trial has been open.
	Director of Clinical Trials and Research	5.2	Provide a summary of review based on accrual status to the Director of Clinical Trials and Research within 5 working days. **NOTE:** Trials that have not accrued 20 percent of target accrual for each year the trial has been open to accrual will be closed.
	Director of Clinical Trials and Research/IRB or designee	5.3	Provide a summary of review and notice (Closure Letter – ***see Attachment D***) to the PIand Clinical Trials Manager within 5 days of review that the trial will be closed.
	Regulatory Staff CTO	5.4	Submit a final report or amendment to close trial to accrual to the IRB. **NOTE:** COV shall be scheduled, if applicable (e.g.

			Industry sponsored Trials) prior to Final Report submission

RESOURCES:
N/A

Endorsed by: Tracy Butryn, Director of Clinical Trials
Manny Changalis, IRB Vice-Chair

Approved by: Jeff Jahre, Senior Vice President of Medical Affairs
Donna Sabol, Vice President and Chief Quality Officer

ATTACHMENT A

St Luke's HOSPITAL & Health Network

New Study Feasibility Checklist

Trial Title:				
Department:				
Sponsor:				
SLHN PI:		IVRS ☐	EDC ☐	Imaging ☐
SLHN Co-I:		IVRS ☐	EDC ☐	Imaging ☐
Lead Research Coordinator:		IVRS ☐	EDC ☐	Imaging ☐
Backup Research Coordinator		IVRS ☐	EDC ☐	Imaging ☐
Pharmacist		IVRS ☐	EDC ☐	Imaging ☐
Data Manager		IVRS ☐	EDC ☐	Imaging ☐
Laboratory Coordinator		IVRS ☐	EDC ☐	Imaging ☐
Key Personnel ***everyone listed must have CITI & FCOI training***		IVRS ☐	EDC ☐	Imaging ☐
Treatment locations/campus' (e.g. where IP will be given)				
Additional non-treatment research locations (e.g. imaging, labs, physical exams)				
Location of IP drug storage:				
When will drug be shipped?	Per Patient ☐	Upon First Patient Enrolled ☐	Upon Activation ☐	
Patient Payments?	Yes ☐ No ☐			
	If yes, number of onsite visits:			

***Please Note*: Trials REQUIRING the use of a central IRB in lieu of the SLHN IRB CANNOT be done at SLHN**

Study Summary

Study Objective Short description of the study/protocol intended for the lay public. Include a brief statement of the study	

hypothesis.	
General Eligibility Criteria **Interventional Studies:** Summary criteria for participant selection. The preferred format includes lists of inclusion and exclusion criteria. **Observational Studies:** Study Population Description: A description of the population from which the groups or cohorts will be selected (e.g., primary care clinic, community sample, residents of a certain town).	

Study Characteristics

Does this trial address an area where we currently have no treatment option or need an additional clinical trial option? Yes ☐ No ☐

If No, Describe how study differs from current options:

Does this trial compete with an existing or pending trial? Yes ☐ No ☐

If Yes, provide priority list including the competing trials and provide justification why this trial should be opened.

Does the use of the investigational agent(s) in this protocol require an application to and approval by the BRANY Institutional Biosafety Committee (IBC)?	Yes	☐	No	☐
If Yes,				
○ Recombinant DNA not exempt by the NIH Guidelines or requiring Biosafety Level or above (this includes transgenic plants and animals)	Yes	☐	No	☐
○ Infectious Agents including:				
▪ Human blood, body fluids, or unfixed tissue	Yes	☐	No	☐
▪ Tissues, organs or cell cultures of human origin	Yes	☐	No	☐
▪ Human Gene Transfer	Yes	☐	No	☐
Does the protocol call for the submission of pathology blocks?	Yes	☐	No	☐
If Yes, please contact Pathology to determine if this is feasible				
Does the protocol require extra radiology tests or procedures?	Yes	☐	No	☐
If Yes, separate arrangements will need to be made with Radiology				
Does the protocol utilize a central or local lab?	Central	☐	Local	☐
Does the protocol require correlative PKs?	Yes	☐	No	☐
Is PI credentialing required?	Yes	☐	No	☐
Is Radiation Safety Committee review/approval required?	Yes	☐	No	☐
Does this trial utilize an Investigational Device?	Yes	☐	No	☐
a) *If Yes, answer the following:*				
i. Will the device be supplied by the sponsor or purchased? _____				
ii. Will the device require storage space?	Yes	☐	No	☐
1. If yes, *Where will the device be stored?* _____				
Does the protocol have any *"Other"* unique requirements that are not listed above?	Yes	☐	No	☐
If Yes, please list_____ & ensure arrangements & contacts are made				

Sponsorship

Is this an Industry Sponsored Trial?	Yes	☐	No	☐
Who is the Contact at the Sponsor?				
Is this a Cooperative Group study (oncology only)?	Yes	☐	No	☐

If Yes, what is the National Target accrual?

Is this an Investigator Initiated Trial? Yes ☐ No ☐

If Yes,

- Who will serve as the lead site (e.g. sponsor) and who is the contact?

Please note: SLHN-sponsored interventional IITs must be discussed with the Tracy Butryn (Max), Director of Clinical Trials before moving forward*

- Is there funding for this trial? Yes ☐ No ☐

Accrual

What is the expected total accrual for SLHN? Patients

Please note: *It will be expected that you enroll at least 20% of this target accrual per year, or the trial shall be reviewed for closure per Accrual Closure Policy (Attached)*

Is the PI and/or Co-I prepared to review and sign off on all required study documents in a timely manner and on a regularly scheduled basis as required by regulatory authorities, the study protocol, and/or institutional policies? Yes ☐ No ☐

Signature of Principal Investigator:

ATTACHMENT B

Accrual Policy Exemption Request

Sponsor: _____

Protocol Number: _____

Title: _____

_____

_____

PI: _____

Reason for Exemption (circle one):

- Rare Disease
- Institutional Priority
- Observational Trial
- Other

  Please Explain: _____
  _____
  _____

PI Signature _____

Department Chair Signature _____

ATTACHMENT C

Exemption Log

PI:	Date:	Study Sponsor & Study Number:	Reason for Exemption:

ATTACHMENT D

St Luke's HOSPITAL & Health Network

February 9, 2011

Dear XXXXXX,

Your trial entitled: "_____" was recently reviewed for accrual as it has been open for at least a year. Per the SLUHN Accrual Closure Policy, all clinical trials supported by the SLUHN Clinical Trials Office must enroll at least 20% of the target accrual per year that the trial has been open for accrual.

Your above referenced trial has been open to accrual for ___ years with ____ patients enrolled, thus not meeting the standards of this policy.

Per the SLUHN Accrual Closure Policy, you are being notified that the above referenced trial is to be permanently closed to accrual (if there are subjects being followed) or terminated with the IRB (if there are no subjects being followed) as your trial has fallen into one of the following three categories:

1. It has been 1 year since you were granted an extension of your trial and the accrual has still not met the standards of the SLUHN Accrual Closure Policy
2. Your trial is not exempt from this policy and has been open for greater than two years with zero accrual
3. Your trial was granted an exemption from this policy, but has been open for greater than three years with zero accrual

Thank you in advance of your support of this policy that recognizes an increased risk for subjects on clinical trials that are not likely to meet their objective in 5 years, as well as the resources needed to support the ongoing maintenance of clinical trials.

Sincerely,

Stanislaw Stawicki, MD

Chair, Research and Innovation
IRB Medical Director

Tracy Butryn, MS, CCRP, CHRC

Director of Clinical Trials and Research